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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/679,258	10/07/2003	Francesco Orlandi	51637/76	3122

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EXAMINER	
CLOW, LORI A	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/679,258	ORLANDI ET AL.	
	Examiner	Art Unit	
	Lori A. Clow, Ph.D.	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-30 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-30 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/27/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 1-30 are currently pending.

Specification

The disclosure is objected to because of the following informalities: On page 2, line 7, there is a spelling error. "Quire" should be changed to "quite". On page 9, lines 28 and 29, there is another spelling error. "Guassian" should be changed to "Gaussian".

Appropriate correction is required.

Claim Objections

Claim 1 is objected to because of the following informalities: Claim 1 recites "BPD/OFD ratio". These terms should be spelled out at least the first time that they are used in the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for assessing a patient's risk of having a fetus with Down's syndrome or spina bifida, does not reasonably provide enablement for assessing a patient's risk of having a

fetus with **any** fetal abnormality. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must be able to assess a patient's risk of having a fetus with any fetal abnormality, comprising testing bi-parietal diameter to occipito-frontal diameter ratio and a secondary marker measurement. For the reasons discussed below, this constitutes undue experimentation.

b) and c) The specification provides examples for assessing a patient's risk of having a fetus with Down's syndrome but does not provide examples for assessing risk of having any fetal abnormality, such as phenylketonuria (PKU), Tay-Sachs, or any other known fetal abnormality. The specification begins with an introduction in which the background of Down's syndrome diagnosis is outlined (pages 1 and 2). The specification goes on to list several fetal markers, both biochemical and ultrasonographic, such as those for Trisomy 13, 18, 21, OSB, Turner Syndrome, and Triploidy (page 6). However, the specification does not describe which markers may be used in conjunction with the cephalic index for any of these defects. The specification next

describes how a priori risk is determined for Down's syndrome (page 12 and 13). Finally, beginning at page 16, the specification provides a working example in which the risk of having a fetus with Down's syndrome is analyzed using BPD/OFD ratios, hCG, PAPP-A, and nuchal translucency as markers, citing various prior art references that outline Down's Syndrome studies. The specification, however, fails to teach what markers to use in conjunction with any other fetal abnormality such that a meaningful result would be attained.

d) The claims are drawn to methods of assessing risk of **any** fetal abnormality with the BPD/OFD and a secondary marker.

e) and g) It would have been well known in the art at the time of invention that determination of the bi-parietal diameter or occipito-frontal diameter in conjunction with a secondary marker was useful in the assessment of certain fetal abnormalities, such as Down's syndrome. For example, Bromley et al. (Journal of Ultrasound in Medicine (2000)Vol. 21, pages 1087-1096) describe the benefits of the "genetic sonogram" for determining the risk of Down's syndrome in fetuses using Bayes theorem and likelihood analysis (see abstract). In the study, various markers, such as nuchal fold and bi-parietal diameter were measured to identify potential structural fetal anomalies (see Methods). However, the art is silent as to detecting other types of fetal abnormalities, such as PKU.

f) The skill of those in the art of molecular biology is high.

h) The claims are broad because they are drawn to assessing the risk of any fetal abnormality. The skilled practitioner would first turn to the instant specification for guidance to practice methods. However, the instant specification does not provide specific guidance to practice these embodiments. As such, the skilled practitioner would turn to the prior art for such

guidance, however, the prior art shows that such assessments using bi-parietal diameter can detect only certain abnormalities, and require substantial additional work and research. Finally, said practitioner would turn to trial and error experimentation to elucidate specific markers for specific abnormalities that could be used in conjunction with sonographic techniques, such as measurement of the BPD/OFD ratio, if they could be used at all. Such represents undue experimentation.

Claim Rejections - 35 USC § 112-2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "comparison of the BPD/OFD ratio...and at least one secondary marker". Which secondary marker measurement is intended? Clarification is requested.

Claims 1 and 28 recite "a priori risk". This was not calculated in the steps of the claim and it is unclear from where this risk comes. Clarification is requested.

Claim 14 recites "deriving a set of likelihood ratios". It is unclear from where these ratios are derived. Clarification is requested.

Claim 14 recites "for pre-determined categories". There is insufficient antecedent basis for this in the claims. Clarification is requested.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,573,103 B1(Wald), further in view of Stempfle et al. (Pediatric Radiology (1999) Vol. 29, pages 682-688).

The instant claims are drawn to a method of assessing a patient's risk of having a fetus with fetal abnormality comprising determining BPD/OFD ratio, determining a secondary marker, performing a comparison of the BPD/OFD ratio and the secondary marker to relative frequency distributions obtained from known affected and unaffected pregnancies, thereby assessing a patient's risk of having a fetus with a fetal abnormality.

In regard to claims 1-5 and 7-30, Wald teaches a method for screening for fetal Down's syndrome in which marker levels are measured in order to calculate risk of Down's syndrome(chromosomal abnormality/trisomy 21) (abstract). In particular, Wald teaches assaying a sample obtained from a pregnant woman at a first stage of pregnancy from at least one biochemical screening marker and/or from at least one ultrasound screening marker, assaying a sample obtained from a pregnant woman at a second stage of pregnancy from at least one biochemical screening marker and/or from at least one ultrasound screening marker, and determining the risk of Down's syndrome using the markers levels. The risk may be determined by a statistical analysis based upon reference data derived from existing or future studies (column 2, lines 5-32). Wald also teaches that this method may be used with AFP in screening for open neural tube defects (spina bifida) (column 2, lines 66-67 to column 3, lines 3) (1-5, 29 and 30).

The biochemical markers can include AFP, hCG, PAPP-A, and others listed at column 4, lines 51-67. The ultrasound markers can include nuchal translucency thickness, nuchal fold thickness, femur length and others listed at column 5, lines 1-12 (7-11).

Wald teaches that the single risk estimate in the invention is derived from measurements of marker levels carried out on biochemical samples and/or utlrasound images which are

obtained sequentially at two or more different stages of pregnancy. The calculation can be integrated as a single test at one stage (column 5, lines 26-31).

Calculation of risk from the measured marker levels is based upon the relative frequency distribution of marker level in Down's syndrome (affected) and unaffected pregnancies. Any of the known statistical techniques may be used, but the multivariate Gaussian model is preferred (column 6, lines 19-column 9) (claims 12-16).

Standard deviations, correlation coefficients, and means (MoM) for unaffected and Down's syndrome pregnancies for screening markers (based on the gestational age estimate using ultrasound scan examination, with maternal weight adjustment of serum markers (normalization) is depicted in Table 1 (claims 17-18).

The multivariate Gaussian analysis of the MoM for all markers from each stage of pregnancy is performed to give distribution parameters, which may then be used for assessing overall risk or age-specific risk (column 13, lines 14-43) (claims 19-27).

Screen positive and screen negative evaluations can be determined from the various implemented steps described above based upon evaluation cut-off values (column 13) (claim 28).

Finally, Wald teaches that this process can be automated (abstract and column 3, lines 33-43) (claim 30).

Wald does not specifically teach using the ultrasound marker BPD/OFD in the evaluation of patient risk for having a fetus that is abnormal (step 1 of claim 1 and dependent claims, claims 28-30). However, Stempfle et al. do teach that biometrical and morphological criteria have been used in fetal screening of Down's syndrome. More specifically the bi-parietal diameter/occipto-

frontal diameter ratio (BPD/OFD) has been employed in numerous studies as an indication of trisomy 21 (see abstract and see page 686, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to use the ultrasound marker of BPD/OFD ratio of Stempfle et al. in the methods taught by Wald, as the primary marker. Wald motivates one to utilize such a marker at column5, line 5, where he lists a series of ultrasound imaging markers and states that "measurements carried out on ultrasound images may include one or more of the following ultrasound markers of Down's syndrome, among others", thus also providing one with a reasonable expectation of success in using any known ultrasound marker.

No claims are allowed.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center Number is (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward, Ph.D., can be reached on (571) 272-0722.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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December 13, 2004
Lori A. Clow, Ph.D.
Art Unit 1631
Lori A Clow

MARJORIE MORAN
PATENT EXAMINER
Marjorie A Moran
12/13/04